Environmental Toxins and Breast Cancer on Long Island. II. Organochlorine Compound Levels in Blood[1]

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Abstract

Whether environmental contaminants increase breast cancer risk among women on Long Island, NY, is unknown. The study objective is to determine whether breast cancer risk is increased in relation to organochlorines, compounds with known estrogenic characteristics that were extensively used on Long Island and other areas of the United States. Recent reports do not support a strong association, although there are concerns with high risks observed in subgroups of women. Blood samples from 646 case and 429 control women from a population-based case-control study conducted on Long Island were analyzed. No substantial elevation in breast cancer risk was observed in relation to the highest quintile of lipid-adjusted serum levels of *p,p′*-bis(4-chlorophenyl)-1,1-dichloroethene (DDE) [odds ratio (OR), 1.20 *versus* lowest quintile; 95% confidence interval (CI), 0.76–1.90], chlordane (OR, 0.98; 95% CI, 0.62–1.55), dieldrin (OR, 1.37; 95% CI, 0.69–2.72), the sum of the four most frequently occurring PCB congeners (nos. 118, 153, 138, and 180; OR, 0.83; 95% CI, 0.54–1.29), and other PCB congener groupings. No dose-response relations were apparent. Nor was risk increased in relation to organochlorines among women who had not breastfed or were overweight, postmenopausal, or long-term residents of Long Island; or with whether the case was diagnosed with invasive rather than *in situ* disease, or with a hormone receptor-positive tumor. These findings, based on the largest number of samples analyzed to date among primarily white women, do not support the hypothesis that organochlorines increase breast cancer risk among Long Island women.

Introduction

Residents of Long Island, New York, have long been concerned about the effects of environmental pollutants, particularly the widespread spraying of the persistent organochlorine pesticide DDT[3] (1), which was used on Long Island primarily for control of mosquitoes and gypsy moths before its ban in the United States in 1972. These concerns, coupled with the community's more recent focus on the high incidence rates of breast cancer observed in Nassau and Suffolk counties[4] (2), led to federal legislation mandating that an epidemiological study be conducted to address these and other environmental health issues (Public Law 103-43, June 10, 1993).

Organochlorines (DDT and its metabolite DDE, the industrial chemical PCBs, the termiticide chlordane, the pesticide dieldrin, and others), have known estrogenic and antiestrogenic characteristics *in vivo* and *in vitro* (3). The important influence of estrogen in breast cancer development (4, 5) suggests that exposure to these contaminants, which have been classified as either known or suspected carcinogens, could affect the initiation or promotion of breast carcinogenesis (3, 6–8).

An increased risk of breast cancer in relation to organochlorines was observed in several early as well as later reports (9–16). However, most epidemiological studies (17–35), including others in the Long Island-New York City area (36–38), have not been strongly supportive of a relationship between DDT or PCBs and the incidence of breast cancer. Remaining concerns include recent reports of subgroup effects that become

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[3] The abbreviations used are: DDT, bis(4-chlorophenyl)-1,1,1-trichloroethane; DDE, bis(4-chlorophenyl)-1,1-dichloroethene; PCB, polychlorinated biphenyl; CV, coefficient of variation; OR, odds ratio; CI, confidence interval; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.

[4] Cancer incidence and mortality by county, 1992–1996, New York State (1999). Internet address: http://www.health.state.ny.us/nysdoh/cancer/volume1.htm.

Table 1 Number of blood samples selected for organochlorine compound assays by case-control status and by reason for selection, Long Island Breast Cancer Study Project, 1996–1997

	Subject status	Cases (*n*)			Controls (*n*)	Total (*n*)
		Invasive	*In situ*	All		
(A)	Respondent to main questionnaire			1508	1556	3064
(B)	Blood donor			1102	1141	2243
(C)	Blood samples selected for organochlorine compound assays (= E + F)	601	184	785	429	1214
(D)	Reason for selection:					
(E)	Random sample[a]	415		415	406	821
(F)	Specifically selected (= G + H + I + J + K)	186	184	370	23	393
(G)	*In situ* cases selected		128			128
(H)	African Americans not randomly selected	5			23	28
(I)	Selected as *in situ*, but invasive	42				42
(J)	Selected as invasive, but *in situ*		56			56
(K)	Donated second sample	139				139
(L)	Blood samples included in most statistical analyses (= C − K)[b]	462	184	646	429	1075

[a] All of the samples donated by *in situ* cases with sufficient amounts of blood/DNA were selected for analyses (see "Materials and Methods").
[b] Excludes second samples (see "Materials and Methods").

evident when the association between breast cancer and organochlorines is stratified by breastfeeding history (39, 40), menopausal status (16), or body size (33) and when cases are categorized on selected characteristics of the tumor, such as stage of disease (41) or hormone-receptor status (12), or with selected exposures including specific PCB congeners (15, 37, 39, 42) or dieldrin (23). The study reported here is based on data collected as part of the Long Island Breast Cancer Study Project, a population-based case-control investigation (43) with large numbers of biological samples available for analyses to facilitate exploration of possible subgroup effects.

Materials and Methods

The investigation was undertaken after approval from participating institutional review boards and in accordance with an assurance filed with and approved by the United States Department of Health and Human Services. Details of the study methods have been described previously (43).

Study Subjects. Eligible cases included female residents of Nassau and Suffolk counties, age 20 years or older, who spoke English, and were newly diagnosed with *in situ* or invasive breast cancer between August 1, 1996, and July 31, 1997. Cases were identified through pathology laboratories of all of the hospitals in the Long Island area. Controls were female residents of the same two counties and were frequency matched by 5-year age group to the expected age distribution of the cases. Controls were identified using random digit dialing (44) for those under age 65 years, and Health Care Financing Administration rosters for those ages 65 years or greater.

Participants included 1508 cases and 1556 controls. Excluding unlocatable women (for whom final study eligibility could not be determined), the overall interview response rates are 83.2 and 68.0%, respectively. Participants ranged in age from 24 to 96 years, and the proportion who identified themselves as white was 93%; 5% were black, and 2% were other; 4% of participants also identified themselves as of Hispanic ethnicity, regardless of race (43).

Exposure Assessment. Signed informed consent was obtained from each participant prior to data collection. The 2-h questionnaire was administered in person by a trained interviewer. Nearly three-quarters of case and control participants who completed the main interview donated a nonfasting blood sample (73.0 and 73.3%, respectively). A sample of cases with invasive cancer who provided a prechemotherapy blood sample also donated a second, postchemotherapy, sample ($n = 139$, or 88.0% of the women approached), because of an earlier concern regarding the effect of chemotherapy on organochlorine levels (45).

In a previous analysis (43), established risk factors for breast cancer that were also found to increase breast cancer risk among Long Island residents included lower parity, late age at first birth, little or no breast feeding, and family history of breast cancer. These same factors were found to increase the risk for breast cancer among respondents who donated blood (data not shown). Factors that were found to be associated with a decreased likelihood that a respondent would donate blood include increasing age (1% decrease for each yearly increase in age) and past smoking (25% decrease); factors associated with an increased probability include white (65% increase) or other race (74% increase), alcohol use (28% increase), ever breastfed (47% increase), ever use of hormone replacement therapy (63% increase), and ever had a mammogram (51% increase). Case-control status was not a predictor of blood donation among respondents (43).

Subjects Selected for Laboratory Assays of Organochlorines. Blood samples were randomly selected for the laboratory assays from among participants who donated a sample with a serum blood volume of >1.5 ml. As shown in Table 1, the number of samples randomly selected included 415 cases with invasive breast cancer and 406 controls. All of the samples with sufficient blood volume donated by African-American subjects who were not selected during the random selection process were assayed ($n = 5$ cases and 23 controls). All of the 184 cases diagnosed with *in situ* disease who had donated a blood sample were also assayed. Laboratory samples were selected on the basis of the initial case diagnosis. However, by the end of the field activities when the data were more completely characterized, selected blood samples that were originally categorized as donated by cases with invasive cancer were determined to have been donated by women with *in situ* disease ($n = 56$), and those originally categorized as *in situ* were determined to be invasive ($n = 42$). In addition, the second blood samples donated by 139 cases diagnosed with invasive breast cancer were also analyzed.

Laboratory Assays. The method of Brock *et al.* (46) was used to determine serum organochlorine levels including *p,p′*-DDE, *p,p′*-DDT, oxychlordane, *trans*-nonachlor, dieldrin, and 24

PCB congeners (nos. 15, 28, 74, 66, 56, 101, 99, 82, 118, 146, 153, 105, 138, 178, 187, 183, 167, 174, 177, 156, 180, 170, 199, 203). Limits of detection were ~0.2 ng/ml for DDE and DDT and 0.07 ng/ml for individual PCB congeners based on 3 × the SD (47) of the levels found in the lowest quality control plasma pool. When the serum pool and blanks were considered together (48) the limit of detection for the PCB congeners was 0.01–0.1 ng/ml; the instrumental limit of detection based on a peak:noise ratio of 3, was 0.01–0.03 ng/ml for tetra- through hepta-chlorobiphenyls, using 1–1.5 ml of plasma. This estimate is similar to that reported recently in other studies (49). The laboratory was blind with respect to any information concerning study subjects; all individually matched and multiple specimens from the same individual were analyzed in the same laboratory batch. Three serum pools, created from outdated bloodbank plasma, were analyzed for quality control purposes over the course of the analyses. Results were: for the low (unfortified) pool ($n = 95$) DDE 2.3 ng/ml, CV 35%, and PCB (as the sum of the 4 major peaks) 1.6 ng/ml, CV 40%; for the medium pool ($n = 66$) DDE 16 ng/ml, CV 15%, and PCB 6.0 ng/ml, CV 26%; for the high pool ($n = 35$) DDE 28 ng/ml, CV 10%, and PCB 13 ng/ml, CV 19%. A medium-level pool was also incorporated into the field samples in a blinded fashion; results for 28 samples were: DDE 14 ng/ml, CV 16%, and PCB 4.2 ng/ml, CV 22%. Similar results were obtained for individual peaks and other organochlorines. Serum triglycerides and cholesterol were determined by a commercial laboratory (Nichols Institute/Quest Diagnostics, Teterboro, NJ).

Statistical Analyses. Positive and zero values of individual organochlorine levels below the detection limit were set to the lowest positive value for that compound observed in these samples, rather than being assigned a censored value. Values judged to be unreliable were coded as missing; the proportion was low but varied with the specific compound (see "Appendix"). Organochlorine values were adjusted for serum lipid levels (triglycerides and total cholesterol) using the method of Phillips *et al.* (50). Organochlorine distributions were skewed (data not shown), and, thus, the values were log transformed on a natural log scale. Comparisons of the paired first and second blood draw among cases with serial blood donations were conducted using the paired *t* test. There were no statistically significant differences ($P > 0.10$) in organochlorine compound levels between samples taken before and after chemotherapy (data not shown). The organochlorine results presented are, therefore, based on the first blood draw of cases with multiple samples or the only blood draw from cases with a single blood sample. The assayed organochlorine levels included in the statistical analyses are *p,p′*-DDE, chlordane (the sum of oxychlordane and *trans*-nonachlor), dieldrin, and the sum of the four most frequently occurring PCB congeners among our sample of Long Island women [Peak-4 PCBs = IUPAC nos. 118, 153, 138, 180, which together represent a mean (±SD) of 49.42% (±7.81%) of the sum of the 24 congeners assayed (total PCBs)]. Statistical analyses were also conducted for the individual four most frequently occurring congeners, Total PCBs, as well as two other PCB groupings, which were grouped based on toxicological activity and occurrence (37, 51). Extended results based on Peak-4PCBs are reported; they did not substantially differ from the results based on other PCB measures (data not shown). For the 85 subjects with missing data on the Peak-4 PCB measure, which was limited to one or two of the congeners, regression analysis was used to calculate the predicted values for the missing congeners from nonmissing values for the other Peak-4 PCB congeners. Results based on the data with imputed values were not materially different from those obtained from the data in which missing Peak-4 PCB values were simply omitted (data not shown), and, thus, the results based only on the former are shown. Similarly, the number of missing values was higher for the DDT values than for the DDE values. Results for DDE were not materially different from those shown for DDT (data not shown), and only the extended results based on DDE are shown. Multiple regression analyses (52) were conducted to determine those factors that best predicted organochlorine levels in blood among the control women.

Statistical comparisons of the geometric means of case and control organochlorine levels in blood were conducted using the unpaired Student *t* test. Unconditional logistic regression was used to determine the ORs, and 95% CIs, for breast cancer in relation to organochlorine compound levels, with adjustments made for age (continuous) and for other potentially confounding factors (52). The risk of breast cancer was estimated in relation to organochlorines with the blood levels categorized by tertiles, quartiles, quintiles, and deciles, and as continuous variables. Results did not vary substantially with the different cut points used (data not shown). Thus, for the main effects of organochlorines, results shown are based on quintiles; and for exploration of possible effect modification, results shown are based on tertiles. To evaluate an apparent dose-response association between breast cancer risk and a specific organochlorine level, tests for trend were performed based on comparing models with and without the exposure variable entered as a continuous variable (53).

Factors considered either as potential predictors of organochlorine compound levels of blood in multiple regression models or as potential confounders in the initial multivariate logistic regression models include: age at reference, age at reference squared, age at menarche, parity, number of live births, lactation, months of lactation, age at first birth, number of miscarriages, history of fertility problems, BMI at reference (defined as date of diagnosis for cases and as date of identification for controls), BMI at age 20, alcohol intake, cigarette smoking, family history of breast cancer in a first-degree relative, history of benign breast disease, oral contraceptive use, hormone replacement use, race, Hispanic ethnicity, education, marital status, religion, county of residence at the reference date, total years of residence on Long Island, and age first moved to Long Island. The final multivariate models shown include those factors that remained in a best fitting model, which was developed by starting with a model that included all covariates and then excluding those that did not improve the overall fit as measured by the −2 log likelihood ratio test (53).

Potential effect modification, on a multiplicative scale, was formally assessed by comparing the multivariate models with and without cross-product terms (53). Potential effect modifiers considered include: BMI at age 20, BMI at reference, breastfeeding history, menopausal status, length of residence on Long Island, and age at reference. To determine breast cancer risk with cases categorized by tumor stage of disease (*in situ versus* invasive), or ER and PR, unordered polytomous logistic regression (53) was performed. Because of the limited number of cases and controls for whom dieldrin assessments were available, extended analyses were not conducted in relation to this compound.

The statistical analyses were based on all of the cases and controls who were randomly selected for the assays, as well as those who were specifically selected. The analyses were repeated restricting the sample to those cases and controls who were randomly chosen to have their blood assayed (*e.g.*, for the

Table 2 Geometric mean (and geometric SD) serum levels of organochlorine compounds unadjusted and adjusted[a] for lipid levels among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Organochlorine compound	Study population size (*n*)		Unadjusted (ng/ml)			Adjusted* (ng/g)		
	Cases	Controls	Cases	Controls	*t* test *P*	Cases	Controls	*t* test *P*
DDE	643	427	4.31 (2.84)	4.07 (2.68)	0.36	671.96 (2.76)	645.74 (2.59)	0.52
DDT	633	418	0.44 (1.84)	0.43 (1.82)	0.54	68.98 (1.83)	69.32 (1.79)	0.89
Peak-4 PCBs	638	423	2.49 (1.72)	2.45 (1.76)	0.68	386.72 (1.69)	391.74 (1.74)	0.70
BZ118	638	423	0.35 (2.05)	0.36 (2.08)	0.98	55.13 (2.00)	56.47 (2.03)	0.59
BZ138	638	423	0.53 (2.56)	0.53 (2.53)	0.94	82.08 (2.54)	84.92 (2.52)	0.56
BZ153	638	423	0.98 (1.69)	0.96 (1.72)	0.61	151.68 (1.66)	153.20 (1.70)	0.76
BZ180	638	423	0.51 (1.79)	0.49 (1.83)	0.25	79.66 (1.75)	78.63 (1.79)	0.70
Chlordane	597	397	0.61 (2.39)	0.60 (2.07)	0.62	94.58 (2.28)	95.90 (1.95)	0.77
Dieldrin	181	148	0.12 (2.41)	0.12 (2.18)	0.83	20.40 (2.34)	21.29 (2.16)	0.64

[a] Adjusted using method 2 as described by Phillips *et al.* (50).

DDE analyses, cases $n = 415$ and controls $n = 406$). Results from these latter models were nearly identical to the former, and are not presented.

Results

In regression models, factors that were found to significantly predict DDE levels in blood among control women included age at reference date, alcohol consumption, BMI at age 20, number of pregnancies, months of hormone replacement use, race, and religion. The comparable factors for DDT were age at reference date, race, and religion, and for Peak-4 PCBs, were age at reference date, number of pregnancies, marital status, race, religion, years of residence on Long Island, weight at age 20, and weight at reference date.

Table 2 shows the geometric means of blood levels of DDE, DDT, Peak-4 PCBs (summed and individually), chlordane, and dieldrin, unadjusted and adjusted for lipid levels by case-control status. Case-control differences in organochlorine levels were minimal. Table 3 presents the age-adjusted and multivariate-adjusted ORs for breast cancer in relation to these same organochlorine compounds. Slightly elevated, but nonsignificant, multivariate-adjusted ORs were noted for the highest quintile, as compared with the lowest, of DDE (1.20; 95% CI, 0.76–1.90), DDT (1.15; 95% CI, 0.74–1.79), and dieldrin (1.37; 95% CI, 0.69–2.72). No consistent elevation in risk was noted with Peak-4 PCBs, or with chlordane. No dose-response relation was evident for any of the organochlorines (test for trend $P > 0.05$).

The association between organochlorines and breast cancer stratified by parity and lactation is shown in Table 4. Among nulliparous women, a >2-fold elevation in risk was noted in relation to the second and third tertiles of chlordane; however, the cell sizes were small and the estimates of effect were unstable. No heterogeneity in risk was noted in relation to the highest levels of DDE, Peak-4 PCBs, or chlordane among parous women regardless of their breastfeeding history.

Whether BMI at reference modified the association between organochlorines and breast cancer risk is shown in Table 5; no substantially elevated risk was observed among women for any level of BMI. In Table 6 are the multivariate-adjusted ORs for breast cancer in relation to organochlorines within strata of age at reference date, menopausal status, and length of residence on Long Island. No substantial elevations in risk in relation to DDE, chlordane, or Peak-4-PCBs were noted for women under age 65 years and over 65 years or among pre- and postmenopausal women. Among women who had lived on Long Island less than 15 years, risks were nonsignificantly increased in relation to the highest tertile of exposure for DDE (multivariate-adjusted OR, 2.13, as compared with lowest tertile, 95% CI, 0.81–5.60) and Peak-4 PCBs (multivariate-adjusted OR, 1.52; 95% CI, 0.64–3.62); CIs are wide indicating that the estimates are unstable. Among women who resided on Long Island for 15 years or longer, no increased breast cancer risks were observed in relation to any of the compounds examined. Also, when other cut points for length of residence were considered, no substantial heterogeneity was observed (data not shown).

Table 7 shows the multivariate-adjusted ORs for breast cancer in relation to organochlorines with the cases grouped by selected characteristics of the tumor. Risk did not vary with stage of disease (*in situ* or invasive). With cases subdivided based on the joint hormone receptor status of the tumor, no substantial elevations were seen among cases with ER+PR+ or ER+PR− tumors. Among cases with ER−PR+ tumors, nearly a 2-fold risk increase was noted in relation to the highest tertile of Peak-4 PCBs, and a 47% risk reduction was noted in relation to chlordane. However, the corresponding CI intervals were wide, and the tests for trend were not statistically significant ($P = 0.64$ and 0.75, respectively). Among case women with ER−PR− breast cancer, a significant decrease was noted in relation to Peak-4 PCBs (multivariate-adjusted OR, 0.46; 95% CI, 0.24–0.90), but the test for trend was not significant ($P = 0.25$).

Discussion

In this population-based case-control study conducted among women on Long Island, there was little evidence of an increased risk of breast cancer in relation to DDE, DDT, PCBs, chlordane, or dieldrin. These findings are consistent with most recent studies that have focused on DDT/DDE, PCBs, or chlordane (17–38), but not all (9–16, 39). Our finding of no relation with dieldrin is inconsistent with the single previous report (23).

Study limitations include a less than optimal response rate among controls, particularly older controls (43), which has been reported by others who conduct population-based studies (54) or studies among older populations (55). We found no striking heterogeneity in risk in relation to organochlorines when stratified by age, which suggests that the higher rate of nonresponse among older controls did not unduly influence our study results. Also, as reported previously (43), an increased breast cancer risk among these Long Island women was noted in relation to several important established risk factors for breast cancer, including lower parity, late age at first birth, little or no breast feeding, and family history of breast cancer.

Table 3 Age-adjusted and multivariate-adjusted[a] ORs and 95% CIs for breast cancer in relation to log-transformed serum organochlorine levels adjusted[b] for serum lipid levels among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Organochlorine compound	Quintile cutpoints (ng/gm lipid)	Cases, *n*	Controls, *n*	Age-adjusted		Multivariate-adjusted[a]	
				OR	(95% CI)	OR	(95% CI)
DDE	<306.91	122	84	1.00		1.00	
	306.91–515.00	110	83	0.84	(0.56–1.26)	0.88	(0.58–1.32)
	515.01–798.24	127	84	0.91	(0.60–1.36)	0.94	(0.63–1.43)
	798.25–1,373.48	123	85	0.82	(0.54–1.25)	0.92	(0.60–1.42)
	1,373.49–11,818.78	150	83	0.95	(0.62–1.46)	1.20	(0.76–1.90)
DDT	<44.79	129	81	1.00		1.00	
	44.79–61.43	96	82	0.72	(0.48–1.08)	0.69	(0.44–1.07)
	61.44–81.20	123	82	0.94	(0.63–1.39)	1.04	(0.66–1.63)
	81.21–108.03	134	82	1.00	(0.67–1.48)	1.16	(0.75–1.80)
	108.03–747.92	133	82	0.97	(0.66–1.44)	1.15	(0.74–1.79)
Peak-4 PCBs	<262.57	134	83	1.00		1.00	
	262.58–325.56	112	83	0.76	(0.51–1.14)	0.76	(0.51–1.15)
	325.57–427.78	132	83	0.87	(0.58–1.29)	0.90	(0.60–1.35)
	427.79–586.74	123	83	0.77	(0.51–1.15)	0.82	(0.54–1.24)
	583.74–3,287.34	126	83	0.72	(0.47–1.10)	0.83	(0.54–1.29)
BZ118	<32.66	134	83	1.00		1.00	
	32.66–46.45	133	83	0.96	(0.65–1.41)	0.96	(0.64–1.42)
	46.46–63.39	109	83	0.74	(0.50–1.11)	0.77	(0.52–1.16)
	63.40–94.94	114	83	0.72	(0.48–1.09)	0.82	(0.54–1.24)
	94.95–1,015.88	136	83	0.79	(0.52–1.20)	0.93	(0.60–1.43)
BZ138	<49.38	117	82	1.00		1.00	
	49.38–81.09	153	83	1.24	(0.84–1.84)	1.26	(0.85–1.88)
	81.10–111.15	129	83	1.00	(0.67–1.49)	1.04	(0.69–1.55)
	111.16–156.22	106	83	0.79	(0.52–1.19)	0.80	(0.52–1.21)
	156.23–936.75	120	83	0.83	(0.54–1.26)	0.96	(0.63–1.48)
BZ153	<103.75	140	82	1.00		1.00	
	103.75–130.02	115	83	0.74	(0.50–1.10)	0.75	(0.50–1.13)
	130.03–170.81	132	83	0.84	(0.56–1.24)	0.85	(0.57–1.27)
	170.82–227.54	107	83	0.64	(0.43–0.97)	0.68	(0.45–1.03)
	227.55–1,130.08	132	83	0.75	(0.50–1.13)	0.86	(0.56–1.32)
BZ180	<51.49	123	82	1.00		1.00	
	51.49–69.70	121	83	0.89	(0.60–1.33)	0.87	(0.58–1.31)
	69.71–87.41	117	83	0.83	(0.55–1.24)	0.81	(0.54–1.23)
	87.42–120.37	128	83	0.88	(0.58–1.32)	0.89	(0.58–1.34)
	120.38–721.29	134	83	0.86	(0.56–1.31)	0.95	(0.62–1.46)
Chlordane	<62.47	109	78	1.00		1.00	
	62.48–85.68	99	78	0.84	(0.55–1.28)	0.88	(0.57–1.35)
	85.69–111.42	107	78	0.89	(0.59–1.36)	0.97	(0.64–1.49)
	111.43–162.47	145	78	1.12	(0.74–1.70)	1.20	(0.78–1.84)
	162.48–473.08	126	78	0.88	(0.56–1.37)	0.98	(0.62–1.55)
Dieldrin	<14.96	37	29	1.00		1.00	
	14.97–20.90	38	27	1.10	(0.55–2.19)	1.19	(0.59–2.41)
	20.91–26.67	32	29	0.87	(0.43–1.75)	0.91	(0.45–1.84)
	26.68–33.45	22	28	0.62	(0.30–1.30)	0.64	(0.30–1.35)
	33.46–179.29	46	29	1.28	(0.65–2.52)	1.37	(0.69–2.72)

[a] DDE, Peak-4 PCB, and individual PCB analyses were adjusted for age, race, history of fertility problems, and history of benign breast disease. Chlordane analyses were adjusted for age, race, history of fertility problems, and gravidity. DDT analyses were adjusted for history of benign breast disease, history of fertility problems, gravidity, and race. Dieldrin analyses were adjusted for age and race.
[b] Adjusted using method 2 as described by Phillips *et al.* (50).

Results from a previous analysis (43) indicated that there were some differences noted among our study participants who donated blood samples as compared with those who did not. Women were less likely to donate blood if they were older or a past smoker, and more likely if they were white, ever used alcohol, ever breastfed, ever used hormone replacement or oral contraceptives, or ever had a mammogram (43). These factors were not found to substantially confound or modify the relation between breast cancer risk and organochlorines in these data, which suggests that the observed differences between blood donors and nondonors did not substantially affect our study results.

A further consideration stems from a recent report of a 3-fold increased breast cancer risk in relation to DDT, as assessed by repeated measurement of serum levels (15). Repeated assessments may better reflect an individual's true body

Table 4 Multivariate-adjusted[a] ORs and 95% CIs for breast cancer in relation to lipid-adjusted[b] log-transformed serum levels of organochlorine compounds stratified by parity and breastfeeding history among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Parity and breastfeeding history	Organochlorine compound	Tertile cutpoints (ng/g lipid)	Cases, *n*	Controls, *n*	Multivariate-adjusted	
					OR	(95% CI)
Nulliparous women	DDE	<458.25	26	19	1.00	
		458.26–951.82	29	9	1.69	(0.59–4.82)
		951.83–11,818.78	25	17	0.75	(0.24–2.40)
	Peak-4 PCBs	<308.34	26	18	1.00	
		308.35–472.45	21	8	1.55	(0.53–4.56)
		462.46–3,287.34	32	19	1.22	(0.42–3.50)
	Chlordane	<79.18	21	22	1.00	
		79.19–125.53	22	9	2.36	(0.84–6.68)
		125.54–473.08	28	11	2.83	(0.93–8.65)
Parous women, never breastfed	DDE	<458.25	89	57	1.00	
		458.26–951.82	105	81	0.82	(0.52–1.28)
		951.83–11,818.78	136	76	1.14	(0.70–1.84)
	Peak-4 PCBs	<308.34	113	64	1.00	
		308.35–472.45	107	77	0.74	(0.48–1.14)
		462.46–3,287.34	107	72	0.79	(0.50–1.26)
	Chlordane	<79.18	83	59	1.00	
		79.19–125.53	100	68	1.02	(0.64–1.63)
		125.54–473.08	119	75	1.03	(0.64–1.65)
Parous women, ever breastfed	DDE	<458.25	87	63	1.00	
		458.26–951.82	53	49	0.66	(0.38–1.13)
		951.83–11,818.78	73	46	0.96	(0.51–1.80)
	Peak-4 PCBs	<308.34	75	56	1.00	
		308.35–472.45	63	52	0.86	(0.51–1.44)
		462.46–3,287.34	73	47	1.12	(0.63–2.00)
	Chlordane	<79.18	74	48	1.00	
		79.19–125.53	64	51	0.77	(0.45–1.31)
		125.54–473.08	65	45	0.79	(0.44–1.44)

[a] DDE and Peak-4 PCB analyses were adjusted for age, race, history of fertility problems, and history of benign breast disease. Chlordane analyses were adjusted for age, race, history of fertility problems, and gravidity.
[b] Adjusted using method 2 as described by Phillips *et al.* (50).

burden over time, given the possible interindividual variations in metabolizing these compounds. In a pilot study that we conducted before the initiation of our large case-control study, low-dose ambient exposures were not found to result in variable intraindividual blood levels over a short-period of time, and a single measurement was determined to be sufficient (56). Organochlorine levels among the United States population have been decreasing over time (34, 57). It is possible that there were substantial variations in exposure levels in the distant past. However, variations in individual metabolism could possibly result in low variability in recently measured organochlorine levels.

Subgroup Effects. In our study, there was no substantial variation in risk in relation to breastfeeding and menopausal status, nor with the cases subdivided by *in situ* or invasive disease. In contrast, significant risk reductions were observed in relation to Peak-4 PCBs for women who were 65 years or older at diagnosis, in relation to chlordane among case women with ER−PR+ tumors, and in relation to PCBs among breast cancer cases with ER−PR− tumors. However, even with our large overall sample size, the number of subjects on whom each of these subgroup effects is based were small, yielding unstable estimates of effect. Furthermore, none of the ERPR subgroups in which reduced ORs were observed were among those that we had hypothesized *a priori* as either potentially high- or low-risk groups. Consequently, their importance is difficult to interpret, and some, or even all, may be indistinguishable from chance.

PCB Congeners. Recent concern has focused on whether breast cancer risk may be elevated in relation to specific PCB congeners or to congeners grouped by biological activity (estrogen-like, antiestrogen-like, or other), rather than a measure that simply sums all PCBs together, which could obscure important associations (3, 49, 51, 58). When individual congeners have been examined, mean differences between cases and controls have been noted for congeners 74, 138, and 183 (38); for 138 and 118 (15, 25), and for 118 and 156 (49). After stratifying by menopausal status, elevated risks have been noted in relation to congeners 105 and 118 among premenopausal women and 170 and 180 for postmenopausal women (40), or among postmenopausal women in relation to congeners 77, 126, and 169 (42). Findings on these or closely correlated congeners have not been corroborated in the data reported here or by others (29, 31, 33–37). Individual PCB congeners are highly correlated with each other (37, 38, 59), which complicates disentangling any risks associated with either individual or grouped congeners (59).

Breastfeeding. The earlier report of an elevated breast cancer risk in relation to serum PCB levels among postmenopausal women with no history of breastfeeding (39) is consistent with the observation that pesticide residues are removed from the breast and excreted in human breast milk during lactation (60). In the data reported here, and by others (31, 33, 34), there was little effect of breastfeeding on the association between organochlorines and breast cancer.

Table 5 Multivariate-adjusted[a] ORs and 95% CIs for breast cancer in relation to lipid-adjusted[b] log-transformed serum levels of organochlorine compounds stratified by BMI among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Tertile of BMI at reference date	Tertile of organochlorine compound	Tertile cutpoints (ng/g lipid)	Cases, *n*	Controls, *n*	Multivariate-adjusted[a]	
					OR	(95% CI)
1 (16.6–24.9)	DDE	<458.25	117	83	1.00	
		458.26–951.82	90	74	0.87	(0.56–1.35)
		951.83–11,818.78	80	52	1.15	(0.67–1.98)
	Peak-4 PCBs	<308.34	90	65	1.00	
		308.35–472.45	96	74	0.96	(0.61–1.52)
		462.46–3,287.34	98	68	1.17	(0.71–1.95)
	Chlordane	<79.18	91	71	1.00	
		79.19–125.53	88	67	1.03	(0.66–1.62)
		125.54–473.08	85	58	1.13	(0.69–1.87)
2 (25.0–29.9)	DDE	<458.25	54	34	1.00	
		458.26–951.82	61	31	1.09	(0.58–2.05)
		951.83–11,818.78	86	47	0.94	(0.49–1.80)
	Peak-4 PCBs	<308.34	70	36	1.00	
		308.35–472.45	57	31	0.77	(0.41–1.45)
		462.46–3,287.34	75	44	0.69	(0.38–1.27)
	Chlordane	<79.18	52	30	1.00	
		79.19–125.53	63	26	1.30	(0.66–2.53)
		125.54–473.08	78	46	0.73	(0.38–1.42)
3 (30.0–62.6)	DDE	<458.25	31	22	1.00	
		458.26–951.82	36	34	0.70	(0.33–1.50)
		951.83–11,818.78	68	40	1.17	(0.54–2.55)
	Peak-4 PCBs	<308.34	55	37	1.00	
		308.35–472.45	38	32	0.72	(0.37–1.39)
		462.46–3,287.34	39	26	0.85	(0.40–1.80)
	Chlordane	<79.18	36	28	1.00	
		79.19–125.53	35	35	0.68	(0.33–1.42)
		125.54–473.08	49	27	1.17	(0.54–2.50)

[a] DDE and Peak-4 PCB analyses were adjusted for age, race, history of fertility problems, and history of benign breast disease. Chlordane analyses were adjusted for age, race, history of fertility problems, and gravidity.
[b] Adjusted using method 2 as described by Phillips *et al.* (50).

Body Size. Wolff and Anderson (61) suggested, based on a pharmacokinetic model, that women with lower BMI had a higher tissue concentration of DDE 1–2 decades earlier. A positive association between current DDE or dieldrin levels and body size has been observed in several studies (19, 21, 25, 62). Wolff and Anderson (61) determined that the half-life of DDE is longer among obese women than leaner women. Furthermore, in a recent population-based study, breast cancer risk in relation to PCBs was higher in obese women (33). Thus, whether organochlorines affect risk particularly among obese or lean women deserves examination. In the data reported here, body size did not appear to influence the relationship between organochlorines and breast cancer risk, which is consistent with results from the most recent report from the Nurses' Health Study (34) but not from one other report (33).

Menopausal Status and Hormone Receptor Status. After age 50, breast cancer incidence rates decline among Japanese women but rise among Western women (63). Recently, the increasing incidence in Westerners has been shown to be restricted to a rise in ER+PR+ tumors (64), which are considered more hormonally sensitive than the other ERPR subtypes (65). Three-quarters of newly diagnosed breast cancers occur among women over age 50 (2); thus, exploration of whether potential estrogen-related environmental risk factors differentially affect women based on menopausal status or hormone receptor status is indicated. An elevated breast cancer risk in relation to organochlorine levels has been observed among postmenopausal women (16) or among cases with ER+ tumors (12). In contrast, a substantial increase in risk was not found among postmenopausal women, older women, or women diagnosed with ER+PR+ or ER+PR− tumors in the data reported here, or by others (20, 24, 34, 36, 37). In our data, an increase in risk was observed among ER−PR+ subtypes in relation to PCBs. The lack of such an association in other reports (34, 36, 37) and the lack of biological plausibility, increases the likelihood that our observation is a chance finding.

Stage of Disease. A recent investigation (41) observed an increased risk of breast cancer among those with lymph node invasion at diagnosis in relation to levels of DDE, DDT, oxychlordane, *trans*-nonachlor, and PCB 153. Because of our efforts to collect blood from cases before the onset of chemotherapy (43), we lacked detailed information on the final diagnosis by stage of disease beyond a classification as invasive or *in situ* disease. In these data, we observed no substantial differences in risk between *in situ* and invasive breast cancer in relation to serum organochlorines, consistent with a recent study by Zheng (31). Another recent study (66) reported a decrease in breast cancer survival among women with higher organochlorine levels. Further examination of the possibility that organochlorines are associated with a more advanced stage of disease and/or a worse prognosis appears warranted.

Table 6 Multivariate-adjusted[a] ORs and 95% CIs for breast cancer in relation to lipid-adjusted[b] log-transformed serum levels of organochlorine compounds stratified by age, menopausal status, and years of residence on Long Island among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Covariate	Organochlorine compound	Tertile cutpoints (ng/g lipid)	Cases, *n*	Controls, *n*	Multivariate-adjusted[a]	
					OR	(95% CI)
Age at reference date						
<65 years	DDE	<458.25	177	129	1.00	
		458.26–951.82	138	113	0.86	(0.60–1.23)
		951.83–11,818.78	106	78	1.15	(0.75–1.76)
	Peak-4 PCBs	<308.34	179	129	1.00	
		308.35–472.45	137	108	0.92	(0.65–1.31)
		462.46–3,287.34	104	79	1.08	(0.72–1.61)
	Chlordane	<79.18	149	113	1.00	
		79.19–125.53	140	102	1.08	(0.75–1.56)
		125.54–473.08	100	83	0.96	(0.63–1.45)
65+ years	DDE	<458.25	25	10	1.00	
		458.26–951.82	49	26	0.81	(0.34–1.98)
		951.83–11,818.78	128	61	0.91	(0.40–2.06)
	Peak-4 PCBs	<308.34	36	9	1.00	
		308.35–472.45	54	29	0.42	(0.17–1.01)
		462.46–3,287.34	108	59	0.42	(0.19–0.96)
	Chlordane	<79.18	30	16	1.00	
		79.19–125.53	46	26	0.95	(0.44–2.06)
		125.54–473.08	113	48	1.26	(0.62–2.56)
Menopausal status						
Premenopausal	DDE	<458.25	110	75	1.00	
		458.26–951.82	72	48	0.95	(0.57–1.57)
		951.83–11,818.78	30	23	0.86	(0.44–1.71)
	Peak-4 PCBs	<308.34	101	73	1.00	
		308.35–472.45	73	43	1.22	(0.74–2.03)
		462.46–3,287.34	36	27	0.94	(0.51–1.74)
	Chlordane	<79.18	91	71	1.00	
		79.19–125.53	68	42	1.35	(0.80–2.28)
		125.54–473.08	32	22	1.11	(0.56–2.17)
Postmenopausal	DDE	<458.25	85	55	1.00	
		458.26–951.82	115	85	0.81	(0.52–1.27)
		951.83–11,818.78	99	112	1.10	(0.70–1.74)
	Peak-4 PCBs	<308.34	109	55	1.00	
		308.35–472.45	113	87	0.59	(0.38–0.92)
		462.46–3,287.34	174	109	0.73	(0.47–1.12)
	Chlordane	<79.18	85	55	1.00	
		79.19–125.53	112	78	0.92	(0.59–1.46)
		125.54–473.08	79	101	1.09	(0.70–1.69)
Years of residence on Long Island						
<15 years	DDE	<458.25	31	28	1.00	
		458.26–951.82	31	19	1.47	(0.66–3.28)
		951.83–11,818.78	40	19	2.13	(0.81–5.60)
	Peak-4 PCBs	<308.34	35	27	1.00	
		308.35–472.45	32	23	1.09	(0.51–2.34)
		462.46–3,287.34	34	16	1.52	(0.64–3.62)
	Chlordane	<79.18	37	23	1.00	
		79.19–125.53	29	22	0.70	(0.31–1.55)
		125.54–473.08	29	14	1.12	(0.46–2.73)
15+ years	DDE	<458.25	171	111	1.00	
		458.26–951.82	156	120	0.76	(0.53–1.08)
		951.83–11,818.78	194	120	0.94	(0.64–1.38)
	Peak-4 PCBs	<308.34	179	111	1.00	
		308.35–472.45	159	114	0.80	(0.56–1.13)
		462.46–3,287.34	178	122	0.83	(0.58–1.20)
	Chlordane	<79.18	142	106	1.00	
		79.19–125.53	157	106	1.09	(0.76–1.56)
		125.54–473.08	183	117	1.06	(0.73–1.56)

[a] DDE and Peak-4 PCB analyses were adjusted for age, race, history of fertility problems, and history of benign breast disease. Chlordane analyses were adjusted for age, race, history of fertility problems, and gravidity.
[b] Adjusted using method 2 as described by Phillips *et al.* (50).

Table 7 Multivariate-adjusted[a] ORs and 95% CIs for breast cancer in relation to lipid-adjusted[b] log-transformed serum levels of organochlorine compounds stratified by selected case tumor characteristics among breast cancer cases and controls, Long Island Breast Cancer Study Project, 1996–1997

Case tumor characteristic	Organochlorine compound	Tertile cutpoints (ng/g lipid)	Cases, *n*	Controls, *n*	Multivariate-adjusted[a]		*P* trend
					OR	(95% CI)	
Stage							
In situ	DDE	<458.25	60	136	1.00		
		458.26–951.82	55	139	0.91	(0.58–1.17)	
		951.83–11,818.78	59	139	1.09	(0.66–1.80)	0.51
	Peak-4 PCBs	<308.34	59	138	1.00		
		308.35–472.45	53	137	0.93	(0.59–1.46)	
		462.46–3,287.34	62	138	1.18	(0.74–1.90)	0.93
	Chlordane	<79.18	67	129	1.00		
		79.19–125.53	50	128	0.75	(0.48–1.18)	
		125.54–473.08	45	131	1.18	(0.82–1.69)	0.02
Invasive	DDE	<458.25	142	136	1.00		
		458.26–951.82	132	139	0.82	(0.58–1.17)	
		951.83–11,818.78	175	139	1.06	(0.73–1.56)	0.92
	Peak-4 PCBs	<308.34	156	138	1.00		
		308.35–472.45	138	137	0.81	(0.58–1.14)	
		462.46–3,287.34	150	138	0.82	(0.57–1.18)	0.21
	Chlordane	<79.18	112	129	1.00		
		79.19–125.53	136	128	0.66	(0.40–1.08)	
		125.54–473.08	167	131	1.28	(0.88–1.88)	0.87
ER-PR status							
ER+PR+	DDE	<458.25	65	139	1.00		
		458.26–951.82	60	139	0.80	(0.51–1.25)	
		951.83–11,818.78	83	139	1.10	(0.69–1.77)	0.94
	Peak-4 PCBs	<308.34	65	138	1.00		
		308.35–472.45	70	137	0.98	(0.63–1.50)	
		462.46–3,287.34	71	138	0.95	(0.60–1.51)	0.28
	Chlordane	<79.18	52	129	1.00		
		79.19–125.53	67	128	1.21	(0.77–1.91)	
		125.54–473.08	74	131	1.14	(0.70–1.84)	0.95
ER+PR−	DDE	<458.25	14	139	1.00		
		458.26–951.82	12	139	0.61	(0.26–1.40)	
		951.83–11,818.78	19	139	0.70	(0.20–2.45)	0.44
	Peak-4 PCBs	<308.34	12	138	1.00		
		308.35–472.45	16	137	1.04	(0.46–2.36)	
		462.46–3,287.34	16	138	0.81	(0.34–1.95)	0.16
	Chlordane	<79.18	10	129	1.00		
		79.19–125.53	14	128	1.39	(0.58–3.32)	
		125.54–473.08	17	131	1.18	(0.48–2.93)	0.1
ER−PR+	DDE	<458.25	7	139	1.00		
		458.26–951.82	7	139	1.05	(0.34–3.21)	
		951.83–11,818.78	7	139	1.24	(0.35–4.37)	0.65
	Peak-4 PCBs	<308.34	6	138	1.00		
		308.35–472.45	7	137	1.42	(0.45–4.50)	
		462.46–3,287.34	8	138	1.94	(0.58–6.50)	0.64
ER−PR+	Chlordane	<79.18	8	129	1.00		
		79.19–125.53	6	128	0.72	(0.24–2.23)	
		125.54–473.08	5	131	0.53	(0.15–1.90)	0.75
ER−PR−	DDE	<458.25	29	139	1.00		
		458.26–951.82	22	139	0.74	(0.40–1.38)	
		951.83–11,818.78	29	139	0.95	(0.48–1.86)	0.47
	Peak-4 PCBs	<308.34	37	138	1.00		
		308.35–472.45	22	137	0.56	(0.31–1.03)	
		462.46–3,287.34	20	138	0.46	(0.24–0.90)	0.25
	Chlordane	<79.18	23	129	1.00		
		79.19–125.53	22	128	1.02	(0.53–1.94)	
		125.54–473.08	30	131	1.37	(0.70–2.66)	0.84

[a] DDE and Peak-4 PCB analyses were adjusted for age, race, history of fertility problems, and history of benign breast disease. Chlordane analyses were adjusted for age, race, history of fertility problems, and gravidity.
[b] Adjusted using method 2 as described by Phillips *et al.* (50).

Appendix Number and percentage of subjects with laboratory values below LOD,[a] judged unreliable, or missing values for the organochlorine and PCB analyses, Long Island Breast Cancer Study Project, 1996–1997

Compound	Total no.	Subjects below LOD[b]		Subjects with unreliable values[c]		Subjects with missing values[d]	
		n	%	*n*	%	*n*	%
DDE	1070	9	0.84	0	0	5	0.47
DDT	1059	9	0.85	0	0	24	2.27
BZ56	960	313	32.60	110	11.46	20	2.08
BZ66	997	211	21.16	110	11.03	15	1.50
BZ74	1037	95	9.16	0	0	7	0.68
BZ82	1046	83	7.93	0	0	0	0
BZ99	1032	107	10.37	0	0	21	2.03
BZ101	1032	139	13.47	0	0	35	3.39
BZ105	1056	388	36.74	0	0	18	1.70
BZ118[e]	1061	10	0.94	0	0	0	0
BZ138[f]	1061	21	1.98	0	0	13	1.23
BZ146	1041	349	33.53	0	0	16	1.54
BZ153[g]	1061	0	0.00	0	0	14	1.32
BZ156	958	317	33.09	0	0	2	0.21
BZ167	1056	689	65.25	0	0	3	0.28
BZ170	1057	123	11.64	0	0	8	0.76
BZ174	1061	509	47.97	0	0	1	0.09
BZ178	1056	628	59.47	0	0	4	0.38
BZ177	1060	457	43.11	0	0	1	0.09
BZ180	1061	6	0.57	0	0	14	1.32
BZ183	1057	337	31.88	0	0	3	0.28
BZ187	1061	25	2.36	0	0	3	0.28
BZ201	1059	245	23.14	0	0	0	0
BZ203	1060	275	25.94	0	0	0	0
Oxychlordane	1048	110	10.50	0	0	8	0.76
Trans-nonachlor	1027	62	6.04	0	0	14	1.36
Mirex	866	606	69.98	0	0	49	5.66
Dieldrin	329	13	3.95	0	0	0	0

[a] LOD, limits of detection.
[b] Limits of detection were 0.2 for DDE and DDT, 0.07 for PCB congeners, and 0.009 for dieldrin.
[c] Coded as 888 by laboratory [M.S.W.].
[d] Coded as 999 by laboratory [M.S.W.].
[e] Missing BZ118 values were imputed for one subject.
[f] Missing BZ138 values were imputed for 78 subjects.
[g] Missing BZ153 values were imputed for nine subjects.

In conclusion, in this large population-based case-control study among women on Long Island, breast cancer risk was not increased in relation to serum organochlorine levels. These observations are consistent with most of the recent studies conducted in the United States (67) and elsewhere. Thus, it seems unlikely that breast cancer risk is associated with organorchlorines when measured close to the time of breast cancer diagnosis. These data do not rule out the possibility, however, that breast cancer risk is elevated by high organochlorine exposures several decades earlier that, through variations in individual metabolism, now measure as low body-burden levels. Also, very limited data recently suggest that breast cancer mortality may be associated with some organochlorine compounds (66). These possibilities require additional research.

Any future research on the role of organochlorines in breast cancer development must take into consideration that these compounds are not complete carcinogens and, thus, probably act in tumor promotion and progression in concert with other cofactors (including tumor initiators, DNA repair insufficiency, and viral exposures), as has been postulated for non-Hodgkin's lymphoma (68). Current measurement of organochlorines in case-control studies probably reflects their activity as late-stage promoters, possibly only within the window of time between postpregnancy to diagnosis (33, 69). To move the field forward, studies should be of sufficient size to examine potential interactions and should include assessment of the potential cofactors with which organochlorines may interact.

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Appendix

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